Claims:

1. A stable non-aqueous single phase biocompatable viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

3. A stable non-aqueous single phase biocompatable viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

4. A stable non-aqueous single phase biocompatable viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

5. The vehicle of claim 1, 3 or 4 wherein said solvent is selected from the group carboxylic acid esters, polyhydric alcohols, polymers of polyhydric alcohols, fatty acids, oils, propylene carbonate, lauryl alcohol, and esters of polyhydric alcohols.

6. The vehicle of claim 1, 3, or 4 wherein said surfactant is selected from the group esters of polyhydric alcohols, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

7. The vehicle of claim 1, 3, or 4 wherein said polymer is selected from the group polyesters, pyrrolidones, esters or ethers of unsaturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

8. The vehicle of claim 1 wherein the ratios of the components are in the range of 40:60 to 60:40.

9. The vehicle of claim 4 wherein the ratios of the components are in the range of about 5% to about 60% for solvent, about 5% to about 40% for surfactant, and about 5% to about 60% for polymer.

10. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is gml, and the solvent is lauryl lactate.

11. The vehicle of claim 10 wherein the ratios of the components are in the range of about 35% to about 45% for solvent, about 5% to about 15% for surfactant, and about 50% to about 55% for polymer.

12. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is polysorbate, and the solvent is lauryl lactate.

13. The vehicle of claim 4 wherein the polymer is poly(D,L-Lactide), the surfactant is a Pluronic block copolymer, and the solvent is propylene carbonate.

14. The vehicle of claim 4 wherein the polymer is polyvinylpyrrolidone, the surfactant is myristyl lactate, and the solvent is lauryl alcohol.

a3 15. The vehicle of claim 1, 3, or 4 which comprises an antioxidant.

16. The vehicle of claim 15 wherein said antioxidant is selected from the group consisting of tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate.

17. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

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18. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

19. The formulation of claim 17 wherein said formulation is stable at body temperature for extended periods of time.

20. The formulation of claim 17 which comprises at least about 0.1% (w/w) beneficial agent.

21. The formulation of claim 17 which comprises at least about 10% (w/w) beneficial agent.

22. The formulation of claim 17 wherein said beneficial agent is selected from the group consisting of peptide, protein, nucleotide, hormone, virus, or antibody.

23. The formulation of claim 22 wherein said beneficial agent is a protein.

24. The formulation of claim 17 which is stable at 65° C for at least about 2 months.

25. The formulation of claim 17 which is stable at 37° C for at least about 3 months.

26. The formulation of claim 17 which is stable at 37° C for at least about one year.

27. The formulation of claim 17 which is adapted for use in an implantable drug delivery device.

28. The formulation of claim 17 wherein said vehicle is selected from the group consisting of solvent, surfactant and polymer.

29. The formulation of claim 17 wherein said vehicle comprises an antioxidant.

30. The formulation of claim 17 comprising a beneficial agent which has been dried to a low moisture content prior to incorporation in said formulation.

31. The formulation of claim 17 which is stable after sterilization.

32. A method for preparing the stable single phase viscous vehicle of claim 1, 3, or 4 comprising the steps of (1) blending the ingredients at elevated temperature under dry conditions to allow them to liquify, and (2) allowing the liquid from step (1) to cool to room temperature.

33. A method for preparing the stable formulation of claim 17, 41, or 42 comprising combining the single phase viscous vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature to uniformly disperse the beneficial agent in the vehicle, and allowing the formulation to cool to room temperature.

34. The method of claim 33 wherein at least about 0.1% (w/w) beneficial agent is suspended in said vehicle.

35. The method of claim 33 wherein at least about 10% (w/w) beneficial agent is suspended in said vehicle.

36. A method for treating a subject suffering from a condition which may be alleviated by administration of a beneficial agent comprising administering to said subject a therapeutically effective amount of the formulation of Claim 17.

37. The method of claim 36 wherein said administration is parenteral administration.

38. The method of claim 36 wherein said administration is long-term continuous administration.

39. The method of claim 36 wherein said administration is accomplished by use of an implantable drug delivery system.

40. The method of claim 36 wherein said daily administration continues for a period selected from the group consisting of about 3 months, about 6 months, and about 12 months.

41. The method of claim 40 wherein said daily administration is accomplished using an implantable drug delivery system.

42. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type , wherein the components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

43. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

44. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation can be delivered from an implantable drug delivery

system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

45. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

Claims 1, 3, 4, 5, 6, 7, 8, 15, 17, 18, 32, and 33 have been amended to make it clear that vehicle has at least 2 components that form a non-aqueous single phase biocompatable viscous vehicle and that a formulation with an active agent uses such vehicle. New claims 42, 43, 44, and 45 have been added to further clarify the claims. These amendments are fully supported by the specification. No new matter has been added by these amendments.

To render a claimed invention obvious there must be some teaching, suggestion, or motivation to combine or modify the teachings of the prior art. The Examiner has argued that there is motivation in the three citations. Applicants respectfully argue that these three documents when looked at as whole documents do not motivate a person skilled in the art at the time of the subject claimed invention to produce the claimed invention.

Knepp teaches formulations of an active agent suspended in anhydrous, aprotic, hydrophobic, non-polar vehicles with low reactivity. The vehicles listed in Knepp are mineral oil, perfluorodecalin, methoxyflurane, perfluorotributylamine, and tetradecane. There is a general discussion of ingredients that might be added to the formulations, however the examples in Knepp are all single component vehicles. Example 1 teaches perfluorodecalin, methoxyflurane, or mineral oil. Example 2 teaches perfluorodecalin or mineral oil. Example 3 teaches perfluorodecalin or methoxyflurane. Example 4 teaches perfluorodecalin. Example 5 teaches perfluorodecalin, perfluorotributylamine, or tetradecane. To a person skilled in the art at the time of the subject invention, the Knepp document teaches preparation of formulations using a single component. On page 12 Knepp states that inert components can be added to the finished formulation, however, these inert components are not given in the examples. Applicants respectfully point out that on reading Knepp there is no motivation to combine components to form a non-aqueous single phase biocompatable viscous vehicle, or a formulation utilizing that vehicle.

Roorda teaches aqueous formulations in which an active agent is mixed with a polymeric binder. The polymeric binder is a matrix that retains the biologically active agent. Although there is a mention that the liquids can be aqueous, non-aqueous, or undiluted non-aqueous liquids, all of the examples teach aqueous formulations. Applicants respectfully point out that on reading Roorda there is no motivation to combine components to form a non-aqueous single phase biocompatable viscous vehicle, or a formulation utilizing that vehicle.

Nuwayser teaches formulations in which active agent is incorporated in polymer microparticles that are then ground and coated with a film-forming polymer. These coated microparticles are then suspended in dermatologically acceptable viscous liquid bases. There are no sections of the document labeled as examples in the Nuwayser document, however there are figures. Figure 1 teaches coated microparticles in Vaseline as the base. Figure 2 teaches the active agent in poly-(L)-lactide microparticles in Vaseline as the base. Figure 3 teaches the active agent in polylactide (the base is not listed for this figure). There is a mention in Nuwayser that various bases can be used, and that other ingredients can be added to the formulation. However, all of the figures use one component for preparation of the coated microparticles and Vaseline as the base. Applicants respectfully point out that on reading Nuwayser there is no motivation to combine components to form a non-aqueous single phase biocompatable viscous vehicle, or a formulation utilizing that vehicle.

The Examiner has suggested that a combination of Knepp, Roorda, and Nuwayser renders the claimed invention obvious. Applicants respectfully point out that there must be a motivation to combine or modify the teachings of the prior art. Although Knepp teaches non-aqueous formulations, Roorda teaches using aqueous formulations, and Nuwayser teaches that the base can be either hydrophobic or water soluble depending on the drug. A person skilled in the art

reading these three documents at the time of the subject invention would not get any guidance as to whether to use either aqueous or non-aqueous vehicles. The examples in Knepp, Roorda, and Nuwayser teach use of a single component vehicle. The Examiner has pointed out the use of certain compounds in each of the three cited documents. Applicants respectfully point out that the documents must be looked as a whole without using the benefit of hindsight. One cannot use the subject invention and find parts of the invention in the cited documents. One has to look at the whole document at the time of the subject invention and determine whether a skilled person reading the document would have been motivated to combine or modify the teachings to produce the claimed invention. Applicants respectfully suggest that when looked at as whole documents at the time of the claimed invention, the three documents cited by the Examiner (either singly or combined) do not motivate a person skilled in the art to try multi-component non-aqueous single phase biocompatable viscous vehicles.

Double Patenting Rejections

Claims 1-8, 10 and 12-41 have been provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-8, 10-13 and 14-38 of copending Application No. 09/497,422. As the Examiner stated in the Office Action, this double patenting rejection is provisional since the conflicting claims have not been patented as yet. This issue will be addressed once claims have been patented in the copending Application.

Claims 1, 9 and 11 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4 and 9 of copending Application No. 09/497,422. As the Examiner stated in the Office Action, this double patenting rejection is provisional since the conflicting claims have not been patented as yet. This issue will be addressed once claims have been patented in the copending Application.

Conclusions

For at least the above reasons Applicants believe that all the currently pending claims are allowable and request the Examiner to reconsider and allow this application. Should any questions arise in connection with this Response, or the application in general, the Examiner is respectfully requested to telephone the undersigned attorney so that prosecution may be expedited.

Respectfully submitted,

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Claims:

1. [Amended] A stable non-aqueous single phase biocompatable viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

2. [cancel]

3. [Amended] [The vehicle of claim 1] A stable non-aqueous single phase biocompatable viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

4. [Amended [The vehicle of claim 1] A stable non-aqueous single phase biocompatable viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

5. [Amended] The vehicle of claim [2] 1, 3 or 4 wherein said solvent is selected from the group carboxylic acid esters, polyhydric alcohols, polymers of polyhydric alcohols, fatty acids, oils, propylene carbonate, lauryl alcohol, and esters of polyhydric alcohols.

6. [Amended] The vehicle of claim [2] 1, 3, or 4 wherein said surfactant is selected from the group esters of polyhydric alcohols, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

7. [Amended] The vehicle of claim [2] 1, 3, or 4 wherein said polymer is selected from the group polyesters, pyrrolidones, esters or ethers of unsaturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

8. [Amended] The vehicle of claim [2] 1 wherein the ratios of the components are in the range of 40:60 to 60:40.

9. The vehicle of claim 4 wherein the ratios of the components are in the range of about 5% to about 60% for solvent, about 5% to about 40% for surfactant, and about 5% to about 60% for polymer.

10. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is gml, and the solvent is lauryl lactate.

11. The vehicle of claim 10 wherein the ratios of the components are in the range of about 35% to about 45% for solvent, about 5% to about 15% for surfactant, and about 50% to about 55% for polymer.

12. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is polysorbate, and the solvent is lauryl lactate.

13. The vehicle of claim 4 wherein the polymer is poly(D,L-lactide), the surfactant is a Pluronic block copolymer, and the solvent is propylene carbonate.

14. The vehicle of claim 4 wherein the polymer is polyvinylpyrrolidone, the surfactant is myristyl lactate, and the solvent is lauryl alcohol.

15. [Amended] The vehicle of claim 1, 3, or 4 which comprises an antioxidant.

16. The vehicle of claim 15 wherein said antioxidant is selected from the group consisting of tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate.

17. [Amended] A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

18. [Amended] A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

19. The formulation of claim 17 wherein said formulation is stable at body temperature for extended periods of time.

20. The formulation of claim 17 which comprises at least about 0.1% (w/w) beneficial agent.

21. The formulation of claim 17 which comprises at least about 10% (w/w) beneficial agent.

22. The formulation of claim 17 wherein said beneficial agent is selected from the group consisting of peptide, protein, nucleotide, hormone, virus, or antibody.

23. The formulation of claim 22 wherein said beneficial agent is a protein.

24. The formulation of claim 17 which is stable at 65° C for at least about 2 months.

25. The formulation of claim 17 which is stable at 37° C for at least about 3 months.

26. The formulation of claim 17 which is stable at 37° C for at least about one year.

27. The formulation of claim 17 which is adapted for use in an implantable drug delivery device.

28. The formulation of claim 17 wherein said vehicle is selected from the group consisting of solvent, surfactant and polymer.

29. The formulation of claim 17 wherein said vehicle comprises an antioxidant.

30. The formulation of claim 17 comprising a beneficial agent which has been dried to a low moisture content prior to incorporation in said formulation.

31. The formulation of claim 17 which is stable after sterilization.

32. [Amended] A method for preparing the stable single phase viscous vehicle of claim 1, 3, or 4 comprising the steps of (1) blending the ingredients at elevated temperature under dry conditions to allow them to liquify, and (2) allowing the liquid from step (1) to cool to room temperature.

33. [Amended] A method for preparing the stable formulation of claim 17, 41, or 42 comprising combining the single phase viscous vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature to uniformly disperse the beneficial agent in the vehicle, and allowing the formulation to cool to room temperature.

34. The method of claim 33 wherein at least about 0.1% (w/w) beneficial agent is suspended in said vehicle.

35. The method of claim 33 wherein at least about 10% (w/w) beneficial agent is suspended in said vehicle.

36. A method for treating a subject suffering from a condition which may be alleviated by administration of a beneficial agent comprising administering to said subject a therapeutically effective amount of the formulation of Claim 17.

37. The method of claim 36 wherein said administration is parenteral administration.

38. The method of claim 36 wherein said administration is long-term continuous administration.

39. The method of claim 36 wherein said administration is accomplished by use of an implantable drug delivery system.

40. The method of claim 36 wherein said daily administration continues for a period selected from the group consisting of about 3 months, about 6 months, and about 12 months.

41. The method of claim 40 wherein said daily administration is accomplished using an implantable drug delivery system.

42. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type , wherein the components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

43. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

44. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation can be delivered from an implantable drug delivery

system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

45. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.